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CLINICAL AND VIROLOGICAL FINDINGS IN CHILDREN WITH ACUTE RESPIRATORY INFECTION SEEN IN THE GRACE-NEW HAVEN COMMUNITY HOSPITAL FROM 1961 TO 1963

SUE YOUNG SOOK KIMM

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CLINICAL AND VIROLOGICAL FINDINGS IN CHILDREN WITH ACUTE RESPIRATORY INFECTION SEEN IN THE GRACE-NEW HAVEN COMMUNITY HOSPITAL FROM 1961 TO 1963

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Bryn Mawr College, 1960

A thesis submitted to the Faculty of the
Yale University School of Medicine
in partial fulfillment of the requirements
for the degree of Doctor of Medicine.

Department of Epidemiology and Public Health
Yale University School of Medicine

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To

the future of the Virus Diagnostic Laboratory when it will be an indispensable laboratory tool for clinicians.

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CONTENTS

INTRODUCTION

Respiratory infections constitute the commonest cause of acute illness in man. The National Health Survey has estimated that more than 215 million respiratory illnesses occur each year at a rate of 1.25 illnesses per person per year and that they are responsible for over 50 per cent of the acute conditions suffered by the citizens of the United States (48). Among children acute respiratory illnesses assume a special clinical significance not only because of the high morbidity but because of the frequent severity of the symptoms, especially when a dramatic clinical manifestation such as croup occurs. The proportion of common respiratory infections due to viruses greatly exceeds that due to bacteria. Various studies indicate that approximately 90 per cent are non-bacteria, and therefore, unaffected by antibiotics. The specific etiology of respiratory infections remains, therefore, of great clinical interest, in terms of classification of illnesses, rational treatment and of possible future preventive measures.

The purpose of the present study is to review the over-all pattern of respiratory infections in terms of clinical as well as laboratory findings in light of the rapidly accumulating information on the viral agents associated with respiratory infection. The observations reported in the present paper were made in

children hospitalized with acute respiratory illnesses at the Grace-New Haven Community Hospital (G-NHCH) from June, 1961, through December, 1963. The cases studied were selected on the basis of the clinical diagnosis as one of the following syndromes: 1. bronchiolitis; 2. croup; or 3. pneumonia. Each clinical syndrome was further subdivided into those cases from which viral agents were isolated and from those where no viral agents were recovered. Some of the cases from the two subgroups yielded bacterial pathogens. Attempts were made to observe any possible role of bacteria in those cases of dual infection with viral agents. It was hoped that the present analysis of the clinical and laboratory data in children with acute respiratory infections would shed further light on this clinically common yet etiologically complex problem.

REVIEW OF LITERATURE

Our present knowledge concerning the respiratory infections of bacterial origin is reasonably well defined and their clinical management is facilitated by the appropriate use of chemotherapeutic agents, but until recently there was relatively little information concerning the non-bacterial pathogens of the respiratory tract and their mode of behavior in the pathogenesis of respiratory illnesses. As late as 1947, Rabe (92), in reviewing the etiology of infectious croup, postulated that 86 per cent of the 347 cases studied were of non-bacterial cause, or of "viral" etiology, and that these non-bacterial agents could not be elucidated until better techniques for their detection were designed. Dingle and co-workers in 1949 (32) could assign a specific etiology to only 3 per cent of the total respiratory illnesses occurring in Cleveland families, despite surveillance for pathogenic bacteria and influenza virus. Stuart-Harris (107) in his book entitled *Influenza and Other Viral Infections of the Respiratory Tract* pointed out that the causes of the majority of human respiratory illnesses still remained to be found. He divided these still undifferentiated illnesses into "febrile catarrh" or acute respiratory disease (ARD), non-bacterial pneumonia, and the "common cold"; the causes to be found presumably were the viruses of febrile catarrh, of primary atypical pneumonia and of common cold.

In recent years there has been an increasing interest in the viral etiology of respiratory infections. With the development and widespread use of tissue culture methods, an increasing number of "new" viral agents have been discovered and associated etiologically with respiratory illnesses. By using the hemadsorption technique originally described by Vogel and Shekokov (113), a new spectrum of viruses has been added to this growing list.

What are some of the recently uncovered viral agents which have been commonly associated with respiratory infections in children? These include the myxoviruses (except for influenza virus discovered in 1932), adenoviruses, respiratory syncytial (RS) virus, reoviruses and even the enteroviruses. Of the myxovirus group, the influenza viruses generally appear during large epidemics, whereas at other times the parainfluenza and others are commonly encountered in sporadic cases or waves of respiratory disease in children.

1. Parainfluenza Viruses - Types 1, 2 and 3

The first isolation of the parainfluenza virus group was the Sendai virus now designated as parainfluenza type 1. This virus was originally isolated in mice inoculated with autopsy specimens from a newborn with pneumonia in 1953 in Japan (78). The significance of this isolation has been in question, since mice in Japan as well as in China are commonly infected with this virus (41,21).

Parainfluenza type 2, the croup associated (CA) virus, was isolated from throat swabs of children with infectious croup by

Chanock in 1955 (16,17). Subsequently Cramblett (27) reported the isolation of a viral agent similar to the CA virus from an infant with croup in 1958. In the same year Beale et al (4) reported isolation of similar agents in Toronto in 10 of 15 children with croup.

Using the hemadsorption technique, Chanock and his group reported the isolation of two new myxoviruses, initially termed type 1 hemadsorption (HA) and type 2 HA* from nursery school children with acute febrile respiratory illnesses (20). The same group further reported (24) on the results of a more extensive study involving 1,738 children in Washington, D.C. Both HA types 1 and 2 viruses (para-3 and -1) were recovered, almost exclusively from patients with respiratory disease, again suggesting that these agents play an etiological role in respiratory illness.

Since the results obtained by Chanock's and his associates' studies (24,89), there have been several reports implicating various types of parainfluenza virus with croup. Vargosko (110) in his study of 47 children with croup reported that parainfluenza type 1 was recovered from 12 of the 16 croup cases with positive virus isolations. The remaining 4 virus positive cases yielded parainfluenza types 2 and 3, adenovirus type 1 and adenovirus type 5. In the same study serologic evidence of infection with

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* Type 1 HA virus and type 2 HA virus were renamed parainfluenza - 3 and parainfluenza - 1 respectively in 1959 (3).

parainfluenza type 1 virus was found in 36 per cent of all patients with croup, and Asian influenza A was associated with 55 per cent of all patients with croup studied during the Asian influenza epidemic, and 19 per cent through the years. The association of parainfluenza viruses and croup was also reported by Kim (75) and by McLean (82,83). In the latter studies parainfluenza-1 was the dominant myxovirus during winters of both 1960-61 and 1961-62, but it was not isolated during late spring or summer.

2. Adenoviruses

Adenoviruses were originally isolated from fragments of surgically removed human adenoids, initially reported by Rowe *et al* in 1953 (102), but the relation of adenovirus to respiratory disease was not then known. Hilleman and Werner in 1954 (53) isolated an agent from army recruits sick with an influenza-like illness, which proved to be similar to that isolated by Rowe. The importance of the etiological association of adenovirus infection with acute respiratory disease and non-cold agglutinin-developing atypical pneumonia in military recruits has been well elucidated by several investigators (49,60,61). During early studies adenoviruses had been isolated from sporadic cases of pneumonia in children (76,105,106). Subsequently there have been several reports of fatal cases of pneumonia in children with the recovery of adenovirus from the lungs (25,3162). Fatal cases of pneumonia in children attributable to adenovirus infection have now been reported in the United States, England, France, Holland, Japan, and China (108). Benyesh-Melnick and Rosenberg reported the

isolation of adenovirus type 7 from a five month old infant with a fatal case of pneumonia (8). The virus was isolated in high titers from the lung, kidney, spleen, liver, as well as from the antemortum serum sample. In some cases of adenoviral pneumonia, a morbiliform rash has been observed as it was the case in the study by Benyesh-Melnick and Rosenberg. It may be also of interest to note that nephritis and rash have been associated with adenoviral infection of the upper respiratory tract in children and adults (25,44,108).

The frequency of infection and illnesses associated with adenoviruses has been studied by several investigators (6,7,68, 69,70,111,115). In a three-year study period, Vargosko *et al* (111) reported that some of the syndromes associated with positive adenovirus isolations in the children with respiratory symptoms were bronchopneumonia, bronchitis, bronchiolitis and croup. The adenovirus types recovered were types 1, 2, 3, 5 and 7. There was no correlation between individual adenovirus type and clinical syndromes among this study group.

3. Respiratory Syncytial Virus

In 1956 Morris and his co-workers described the first recovery of the respiratory syncytial (RS) virus, initially termed chimpanzee coryza agent (CCA), isolated from the respiratory tract of chimpanzees with acute respiratory illness and from a laboratory worker who had been in contact with these animals (85). Chanock and his group reported (23) recovery of a similar virus from an infant with pneumonia and from another infant with croup

in Baltimore, Md., and showed antibody increases among persons with respiratory illness as well as among controls. Since that time, studies carried out by several groups of investigators in Washington, D.C. (22,71,88), Philadelphia (45,51,81,97), and Chicago (5,46), and elsewhere have provided evidence for the etiologic role of the RS virus in respiratory diseases of childhood. Numerous studies reported within past years indicate that RS virus is probably one of the leading causes of respiratory tract illness in early childhood.

As those observed with the parainfluenza or adenovirus illness, infections with RS virus do not present a single clinical syndrome. Instead, the symptoms and signs are referable to all segments of the respiratory tract. The syndromes with which RS virus has been associated are acute upper respiratory illness (URI), bronchitis, bronchiolitis, bronchopneumonia and, rarely, croup. Collaborative studies carried out at the Children's Hospital of Philadelphia and the laboratories at the Merck Institute for Therapeutic Research yielded information on these clinical manifestations of the RS infection (45,51,81,97).

Chanock _et al_ (22) reported the findings from over a two-year study period at the Children's Hospital of the District of Columbia on the evidence for the etiologic association on RS virus and respiratory illness. The virus was recovered significantly more often from infants and children with respiratory illness than from controls free of such disease. The most striking association of RS infection with illness was observed in young

infants with bronchiolitis or pneumonia where the virus recovery rates were 39 and 23 per cent, respectively. Additional evidence associating RS virus with lower respiratory tract illness was provided during an outbreak of infection in a Washington, D.C. welfare nursery, reported by Kapikian _et al_ (71). A total of 40 per cent of the nursery inhabitants developed a febrile pneumonia during a period extending 19 days and an analysis of the virus recovery data indicated that RS virus was etiologically related to such illness.

4. Enteroviruses

Another major group of viruses which plays an important role in clinical illness, generally non-respiratory, however, is the enterovirus group. Although the association of the enterovirus group with respiratory illnesses has not been as extensively studied as the association of the myxovirus or adenovirus with this type of illness, nevertheless, in assessing viral etiology of respiratory infections, this group ought not to be overlooked. Although enteroviruses are known to be associated with undifferentiated febrile illnesses during the summer in temporal association with outbreaks of enteroviral infections, they have not been associated with lower respiratory tract diseases except in rare instances. Lerner and associates recovered Coxsackie A-9 virus from the lung of a 16-month-old girl who died of pneumonia (80). In an outbreak of Coxsackie B-5 virus infections, Siegel and his co-workers isolated this virus from a single stool specimen in a 1-year-old boy with pneumonia (104). Vargosko and associates reported the

relation of Coxsackie B-5 virus to respiratory diseases in children (112). Five per cent of 118 children hospitalized with respiratory illnesses yielded Coxsackie B-5. The illnesses included bronchiolitis, pneumonia and bronchitis. However, the same virus was also isolated from 5 per cent of children without respiratory illness, thereby indicating that lower tract illness was probably not caused by Coxsackie B-5 virus.

Although Coxsackie A-21 virus has been implicated with mild cold-like illness, reported outbreaks of infection have been limited to young men undergoing military training and it does not seem at present to play a role in the respiratory illness of childhood (13,66).

Philipson (91) has reported recovery of U-virus (ECHO-11) from children with croup. Virus was isolated more frequently from the throat than from the feces. Confirmation of these results is necessary before this virus is considered to be an etiologic agent of croup.

Echo 20 was recovered from both throat and rectal specimens of children in an orphanage. The original papers by Cramblett (29,30) indicated a close temporal relation between virus isolation and the onset of cold-like illnesses with low-grade fever in the infected children. However, more definitive evidence for an etiologic association between ECHO-20 infection and mild illness needs to be established at present.

Reovirus group, one of which was formerly known as Echo-10, has been recovered by Rosen and co-workers from children in an

orphanage during an outbreak of infection (100). Virus isolation was statistically associated with mild, febrile respiratory illnesses.

As can be seen from these numerous reports on virus isolation studies, discovering and defining the etiology of acute respiratory disease has become complex with the multiplicity of agents which it is now possible to uncover with modern tissue culture techniques. After an agent is "discovered" and the range of diseases in which the agent can play is "defined," the relative contribution of this particular agent in a given clinical manifestation needs to be elucidated. Also, it has become almost _sine qua non_ that epidemiologic patterns apply only for the time and place of study. Therefore, an agent which is prevalent at one time may not be so at another. The pattern of contributing role each viral agent plays in a given illness is a fluctuating one. Numerous reports on the surveillance for viral agents in respiratory infections have been published in recent years (6,42, 46,54,73,99,116). These reports substantiate the observation that the importance of certain respiratory viruses varies when studies are conducted in different localities and in different years.

With this wealth of newly accumulated knowledge, there is emerging a new concept of viral infection and its clinical manifestation. Whereas the old concepts were based on a specific behavior of certain viruses such as the measles virus causing the measles syndrome or variola virus causing the smallpox syndrome, the newer idea is based on the observation that a number of

different "respiratory disease viruses" can cause a number of clinically distinct illnesses. Conversely, a virus which may cause predominantly non-respiratory illness can sporadically give as a primary clinical manifestation a respiratory illness.

MATERIALS AND METHODS

Clinical Data

The observation of the respiratory infections in the present study extends from June, 1961, through December, 1963. All the hospital charts on the cases from whom viral agents were isolated were carefully reviewed, including the laboratory data such as routine blood count and bacterial cultures of the nose, throat, and blood. All of the bacteriological procedures were performed by Mrs. Mildred D. Fousek, who was responsible for the bacteriological tests done in Rabe's study during 1937-46 (92-94) and also in Hartmann's work for 1947-57 (47). Identification of bacteria was made on the basis of colony appearance, stained smear, and in the case of H. influenza type B, by serological technique. (Quelling test).

Cases were categorized as bronchiolitis, croup or pneumonia according to clinical features as well as roentgenographic studies diagnostic of each of the clinical syndromes chosen for study. The clinical definition of croup as described by Rabe was used in the present study. All cases of bronchiolitis and pneumonia had X-ray studies. Bronchiolitis was diagnosed when, aside from the characteristic clinical signs of obstructive emphysema, there was also a characteristic X-ray finding of hyperaeration with a flattened diaphragm without any infiltrate. Pneumonia was diagnosed

whenever there was any X-ray finding of pneumonitis, either lobar or peribronchial interstitial infiltration.

A total of 297 cases were studied; this included bronchiolitis, croup or pneumonia. Specimens from these 297 patients were received by the Virus Diagnostic Laboratory of the G-NHCH for viral studies. Clinical records were available on 41 of the 45 cases from whom one or more viral agents were obtained. In addition, a selected period, September, 1962, to September, 1963, was arbitrarily chosen. Records of all cases with a presumptive diagnosis of bronchiolitis, croup or pneumonia during this one-year period were studied even though the viral studies failed to reveal any agent. There were 134 cases in the latter group, and records were available on 122. Only 107 of the 122 cases were chosen for this study since the others did not fit into the clinical categories listed.

Virological Studies

Standard laboratory procedures for virus isolation and serologic techniques were used (59). Isolation tests were performed in the Virus Diagnostic Laboratory. Clinical specimens included nose, throat and rectal swabs and feces. Specimens were collected from patients admitted to the hospital with respiratory infection and were stored at 4°C in Hank's balanced salt solution containing 0.5 per cent gelatin and antibiotics (penicillin and streptomycin). Specimens were inoculated into tissue cultures within 24 hours, if possible. Acute-phase serum samples were collected and were stored at -20°C. Convalescent phase sera were collected,

preferably two to four weeks after onset of illness, although in some cases the intervals were shorter.

Tissue Cultures. Rhesus monkey kidney (MK) tissue culture monolayers were used routinely for virus isolation. These were prepared by the standard methods i.e., primary trypsinized MK cells grown in stationary tubes in a medium consisting of Hank's balanced salt solution with 2 per cent calf serum and 0.5 per cent lactalbumin hydrolysate. In addition, Hep-2, human kidney and human amnion cells were used as well as embryonated eggs; the latter was used especially when influenza virus infection was suspected. For hemadsorption test, rhesus MK tissue cultures were maintained in Earle's special balanced salt solution containing 0.07 per cent $NaHCO_3$ (pH 6.8-7.0) and 2 per cent ultra-filtered fetal calf serum (114).

Virus Isolation and Identification. Inoculum was extracted from the swab by washing with the Hank's balanced salt solution and centrifugation at 3,000 rpm for 30 minutes, the supernatant fluid then being inoculated in 0.2 ml amounts into each of the above culture tubes. The tubes were incubated at 36°C. Cytopathic effect (CPE) was checked at 3, 5 and 7 days post-inoculation. When there was CPE, the culture fluid was harvested and subcultured into respective types of cells for further identification. For detection of myxovirus, one tube (MK with Earle's special solution) was tested on the 4th, 7th, and 10th day for the presence of hemadsorption phenomenon by addition of 0.2 ml of 0.5 per cent fresh guinea pig red cells followed by incubation at

4°C for 20 minutes as described by Chanock _et al_ (20).

When an isolate obtained in the MK tissue cultures was suspected to be an enterovirus, neutralization tests were set up against appropriate pools of hyperimmune monkey antisera for poliovirus, Coxsackie or ECHO viruses. As an additional aid to identification and recognition of virus mixtures in dealing with untypable agents, plaque morphology and host cell spectra have been used for preliminary grouping prior to serological identification.

When there was a positive hemadsorption test, identification of the isolates was made either by hemadsorption-inhibition, hemagglutination-inhibition and/or neutralization tests using type-specific antisera.

Adenovirus was tentatively diagnosed by the characteristic CPE in tissue cultures, especially in Hep-2 cell lines. Culture fluid from the tubes with such CPE was harvested after freezing and thawing and the preliminary grouping was accomplished by the complement-fixation test, using a human reference serum. Final identification of specific adenovirus types was made by neutralization tests in tissue culture.

Antibody Determinations. Antibody studies were carried out whenever paired sera were available. This was to confirm a specific infection where a virus had been isolated and also to detect a rising antibody titer in cases where there was no virus isolation.

Paired sera from the cases of respiratory infection were tested for antibody response against parainfluenza types 1, 2, 3, DA, mumps and Influenza types A and B. Hemagglutination-

inhibition (HI) tests were performed in polyethylene panels by methods described by Hsiung, et al (57,58). Four units of viral agglutinin were employed in all tests and a 0.5 per cent suspension of guinea pig erythrocytes was used as the indicator system. Non-specific serum inhibitors were removed with 25 per cent kaolin treatment.

Complement-fixation (CF) tests were performed against adenovirus, reovirus, and respiratory syncytial virus by overnight fixation at $4^{\circ}C$ using two full units of complement (100 per cent hemolysis). CF antigens for adenovirus and reovirus were prepared in the laboratory; respiratory syncytial virus antigen was obtained from a commercial source. Hemolysin sensitized 2 per cent sheep erythrocytes was used as the indicator system.

RESULTS

Virus Isolations and Serological Studies

The results of the virus studies are those obtained from the Virus Diagnostic Laboratory over the period from June, 1961, through December, 1963. Only those viruses implicated in respiratory illnesses were considered, this includes influenza, parainfluenza, RS, adenovirus and enteroviruses. Of the 297 cases with the presumptive daignosis of bronchiolitis, croup or pneumonia, 45 cases or 15 per cent yielded either one or two viral agents.

Seasonal Incidence. In order to study the frequency of respiratory illness as a chief manifestation of a specific viral infection, the seasonal incidence of the over-all virus isolation rates was plotted in the top graph in Fig. 1. As is shown in this graph, the seasonal incidence of the various viral agents varied in that the myxoviruses were most prevalent during the late fall and winter seasons whereas the enteroviruses were isolated primarily during the summer months and the early fall. Adenovirus was isolated only sporadically and did not seem to be associated with any particular season. The bottom graph in Fig. 1 describes the seasonal incidence of only those viruses clinically associated with respiratory illnesses. It can be seen that the clinical cases of respiratory infection with virus isolations

followed the seasonal pattern of virus activities, especially the myxovirus group.

Clinical Syndromes and Virus Recovery. The recovery ratio of viral agents according to clinical syndromes is shown in Fig. 2. Although the cases included only those from which clinical specimens were submitted for viral studies and do not comprise the total number of admissions with such diseases, they do represent, nevertheless, the general trend.* Out of 64 cases of bronchiolitis, 7 cases were associated with viral agents, or 11 per cent. From 97 cases of croup, 17 cases yielded positive virus isolations, or 18 per cent, and from 17 out of 139, or 12 per cent, of cases of pneumonia, viral agents were recovered. Fig. 2 also indicates the seasonal incidence of each clinical category. All three clinical categories were seen most frequently during cold months. The virus recovery rate, in turn, generally followed the over-all seasonal trend of each clinical category.

Isolations of Specific Viruses and Bacteria. Table 1 lists the percentage of cases in which the various viral agents were isolated and the results of the concomitant bacteriological studies. In the 29 cases of bronchiolitis, 3 cases yielded parainfluenza 1 (10.3 per cent) and 3 cases were associated with adenovirus (10.3 per cent). From 1 case (3.4 per cent) RS virus was isolated

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*The percentage of the cases studied in relation to the total number of admissions cannot be obtained since the hospital statistics are not complete as yet. In general the cases studied in this paper do represent the majority of such cases seen at G-NHCH.

although two additional cases were diagnosed by serological test. Of the 52 cases of croup studied 32.6 per cent yielded parainfluenza viruses of which 19.2 per cent was associated with parainfluenza 1, 9.6 per cent with parainfluenza 2, and only 3.8 per cent with parainfluenza 3. Pneumonia was associated with a variety of agents as shown in Table 1. Influenza A_2 virus was isolated once from a 4-month-old baby with pneumonia, whereas 5 cases of pneumonia (7.5 per cent) were associated with para-1, 1 case with para-2 and 2 cases with para-3. Adenoviruses were obtained from 5 cases. In addition, Coxsackie B (2 Coxsackie B_4 and 1 Coxsackie B_5) and ECHO-22 viruses were also isolated. RS virus was not isolated but there was serological indication in that three of the pneumonia cases had significant antibody rises.

Table 1 also lists the isolation of bacterial colonies. From the 29 cases of bronchiolitis, 31 per cent yielded pneumococci. The significance of this is not known since no controls were studied. Croup cases yielded 21.2 per cent pneumococci, 1.9 per cent staphlococci and 7.7 per cent H. influenza type B. Similar per cent of bacteria findings were obtained with pneumonia cases except that the incidence of H. influenza type B was low. No pathogens, viral or bacterial, were isolated from 45 per cent of bronchiolitis cases, 36.5 per cent of croup cases and 31.2 per cent of pneumonia cases.

In certain instances patients yielded more than one agent either with bacteria or with viruses as noted in Table 2.

1. Dual infections with two viral agents.

One case of pneumonia in a two-month-old infant yielded both parainfluenza virus type 2 and an adenovirus. The patient had right upper and middle lobe pneumonia which responded well to symptomatic treatment without the use of antibiotics. In addition, three cases of pneumonia with parainfluenza virus isolation also showed a significant antibody rise against RS virus. A concurrent infection of parainfluenza and RS viruses cannot be excluded.

2. Virus and Bacteria.

From one case of bronchiolitis infected with para-1 virus and 1 case of bronchiolitis with adenovirus infection, pneumococci were recovered. Two cases of croup with para-1 isolation also grew out pneumococci. Three out of 5 pneumonia cases with para-1 isolation, as well as 1 case with para-3 infection, yielded pneumococci. In addition 1 case of pneumonia with adenovirus isolation and 2 cases of pneumonia with Coxsackie B isolation were also infected with pneumococci. One case of influenza A_2 pneumonia and 1 case with para-3 pneumonia yielded pseudomonas. Both of the latter two cases were associated with other underlying diseases such as congenital heart disease and cystic fibrosis.

Antibody Response. Antibody studies were done in 10 cases with virus isolations and in 17 cases from whom no viruses were isolated. Table 3 indicates antibody responses against various agents. In those cases where no viral agents were isolated, there was no rise to any of the parainfluenza group. There were some

heterologous antibody responses against the parainfluenza group in the group with parainfluenza isolation. Both groups, the ones with virus isolations and the ones without virus isolations showed no detectable antibody rises to adenovirus or reoviruses. In fact, there were no measurable antibodies against reoviruses in any of the 27 cases tested. According to the results of antibody studies, the active viral agents during the period of this study were the parainfluenza group and RS virus. It is noteworthy that of the 10 cases yielding a parainfluenza virus, 3 also showed antibody rises to RS virus. The possibility of simultaneous infections with parainfluenza and RS viruses cannot be positively ruled out. Fifteen per cent of the cases without virus isolation showed greater than a four-fold rise to RS but no rise to the other viruses tested.

Clinical Observations

Bronchiolitis. Various clinical signs and symptoms are tabulated in Table 4. As the table indicates, the onset of bronchiolitis was with symptoms referable to the upper respiratory system such as rhinorrhea, coryza or cough, followed by signs of lower respiratory tract involvement. In studying the clinical manifestations, the cases were divided into 2 groups, 1 group with virus isolations and the other without virus isolations. Since the case numbers were not large enough for a statistical evaluation, one can only make gross observations. On the whole, there were no noticeably consistent differences between the symptomatology of the two groups. For bronchiolitis, the most common symptoms were fever, rhinorrhea,

cough and respiratory difficulty. Gastrointestinal disturbances such as vomiting and diarrhea were present in the majority of the cases of bronchiolitis.

Croup. The onset for croup was abrupt with the mean of 1 day of symptoms before admission. The initial symptoms consisted of hoarseness, stridor, cough or barking cough fever, rhinorrhea and respiratory difficulty (Table 5). Gastrointestinal disturbances were not as prominent as in bronchiolitis cases. The cases of croup from whom Hemophilus influenza type B was isolated generally began with "sore throat." Symptoms of fever, stridor, croupy cough and respiratory distress rapidly developed, so that on admission, the children had marked respiratory distress. All children with H influenza type B croup were "toxic" in appearance at the time of admission. The other findings included erythema of the epiglottis, cervical adenopathy, injection of tympanic membranes. Tracheotomy was performed in 6 per cent of cases with virus isolation and 14 per cent of the cases without virus isolation. All the cases with H influenza type B infection had tracheotomy performed immediately after admission.

Pneumonia. The initial symptoms of pneumonia included rhinorrhea, cough, fever, conjunctivitis and respiratory distress (Table 6). These began 3-4 days before admission. Approximately 50 per cent or more of the children hospitalized developed fever and vomiting was often seen as accompaniment with fever. At admission, respiratory distress, nasal discharge, pharyngeal erythema, dullness to percussion and auscultatory findings were most often seen in these

children with pneumonia. In one case from whom virus was isolated, meningism was present and 3 children had splenomegaly.

Age Distribution. Fig. 3 indicates the age distribution according to the clinical categories. The shaded space indicates virus isolations in each age group. It can be seen that bronchiolitis is primarily a disease of infancy and, therefore, the tallest bar is for the age group of less than 1 year. All cases of croup fall under 4 years of age. Pneumonia again has a highest incidence of attack among infants under 1 year of age. The virus isolation rate follows a similar age distribution.

Comparison of Clinical Findings in Virus Positive and Virus Negative Cases. As shown in tables 4, 5, and 6 the clinical symptoms and signs are generally similar and whatever differences may exist superficially, one cannot draw a statistically significant conclusion. Table 7 summarizes some of the clinical findings that were obtained from cases with and without virus isolation. The incidence of each syndrome according to sex is notable in that there was no difference between the male to female ratio in the groups with positive virus isolations and those groups without virus isolation. For bronchiolitis, the male to female ratio was 4:3 in the group with virus isolation, and 4.3:3 in the group without virus isolation. For croup, the male to female ratio (M:F) was 2.4:1 with virus isolations, and 2.3:1 without virus isolation. Pneumonia had 1:1 of M:F in both groups. There was some variation in days of onset and days of hospitalization for each clinical category of disease but insignificant differences were obtained in

the two groups with or withour virus isolations. The WBC counts were variable and the median WBC of each group in the respective clinical categories was on the whole similar to one another.

Approximately 50 per cent of all the cases of bronchiolitis, croup or pneumonia had a recent history of upper respiratory infection among the family members. There were no consistently appreciable differences in the occurrence of the concomitant family illness to distinguish between the group with virus isolations and the group without virus isolations.

Almost 29 per cent of croup cases with virus isolation had a positive family history for croup. Frequently mothers had had croup in their childhood and the siblings of the patients had previous attacks of croup. In the cases of croup without virus isolation 14 per cent gave a positive family history, only half the incidence in comparison with the group from whom virus was isolated. Twelve per cent of the children with croup from whom virus was isolated had previous attacks of croup, and 23 per cent of these without virus isolations had croup in the past.

It is interesting to note that the allergic history is consistently greater in those groups where no viruses were isolated than among those with positive virus isolations. Of the 29 patients with bronchiolitis with virus isolation studied, 14 per cent had positive allergic history* whereas 27 per cent without

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* Allergic history here includes personal as well as family history of asthma, hay fever or urticaria.

virus isolations had allergic history. But in the croup cases only 6 per cent had allergic history in the group with virus isolation and 17 per cent in the group without virus isolation. The incidence was 0 and 22 per cent in the cases of pneumonia with and without virus isolation respectively.

The underlying diseases included 14 per cent congenital heart disease for those cases of bronchiolitis with virus isolation and 9 per cent of asthma among those from whom no virus had been isolated. No underlying disease was associated with croup cases. The most frequently encountered underlying diseases among those children with pneumonia included 19 per cent congenital heart disease in the group with virus isolation and 6 per cent in the group without virus isolation. Cystic fibrosis was seen in 6 per cent of the group with virus isolation and 4 per cent in the group without virus isolation. In the group without virus isolation 8 per cent of the children had asthma.

Mortality for the bronchiolitis group with positive isolation was an astonishing 14 per cent but this might have been due to the fact that all these patients had congenital heart disease and were in cardiac failure when they entered the hospital. There was no mortality among the children hospitalized with croup. There was no mortality in the cases of pneumonia associated with viral agents and 4 per cent mortality in those without virus isolation. However, all of the latter cases had other underlying diseases such as congenital heart disease or glioma.

DISCUSSION

The number of cases in this investigation is not large enough to attempt to differentiate between symptoms and signs according to different viral agents. Rabe categorized three separate etiologic agents for infectious croup based on distinctive clinical features as well as bacteriologic studies (92-94). In the present study grossly there does not appear to be any difference in the clinical symptomatology among different viral agents. A similar observation was reported by Parrott on the clinical features of infection with hemadsorption viruses (89).

The patterns of distribution of various symptoms and clinical signs in each subgroup of the clinical syndromes, i.e., with virus isolations and without virus isolations, as shown in Tables 4, 5, 6, did not show any consistent difference. In general, they were quite similar to each other within each clinical category subdivided.

The admission WBC counts were extremely variable both in the groups with virus isolations and in those without virus isolations. However, the median figure generally tended to be higher in the groups without virus isolations. One exception was in bronchiolitis where the median WBC was higher in the group with virus isolations. Since leucocytosis has been traditionally implicated with bacterial illness, the incidence of bacterial

infections in the virus negative groups was investigated. If one looks at the isolation rates of bacterial colonies in the three clinical categories, they do not differ significantly except for H. influenza type B, which occurred in a higher frequency in croup. Obviously, WBC responses in young children are extremely variable and cannot be relied upon in differentiating between bacterial and non-bacterial infections.

The role of bacteria in respiratory diseases is often questioned in light of the confusion arising from the definition of "normal" flora of the respiratory tract. In adults, one may generally define the bacterial etiology by the WBC response and the differential count as well as the sputum culture for bacteria, in addition to a typical clinical picture pointing toward an acute bacterial infection. In infants and young children, the role of bacteria is sometimes less evident in the absence of such clear-cut clinical manifestations. In addition, viral agents seem to play a more prominent role in the respiratory illnesses of early childhood as shown by Rabe in his study where 86 per cent of infectious croup was due to "viral" agent or agents (92). Hartmann's series revealed 92 per cent of infectious croup of non-bacterial origin (47). After reviewing routine cultures of the rhinopharynx in 1,350 children, Rabe noted that "even the most extensive form of the disease is little influenced by the rhinopharyngeal flora but instead is dependent upon the primary etiologic agent plus constitutional factors such as age, size of the larynx, duration of immunity" (92). Though this "primary etiologic agent" among young

children seems to be mainly viruses, the possibility of virus plus bacteria cannot be positively ruled out. Eichenwald postulated an attractive theory of synergism between virus and bacteria (34, 36). This speculation, however, needs to be studied further before any conclusion can be drawn.

In discussing the etiology of respiratory infections, it may be unrealistic to do so by different clinical categories since the respiratory tract is a continuous system. The fact that an agent causes croup rather than bronchiolitis may not be entirely due to the particular pathogenicity of the primary causative agent. It must, in part, be due to the combination of the invasive quality of the pathogens involved and the host's response to it. In the frantic search for the villain organisms, the host factors are often forgotten. In viral infections, one of the most important host factors is, of course, the individual's immunological status. Chanock and Parrott have observed that first infection with parainfluenza and RS viruses presumably in an "immunologically virgin individual" is accompanied by a more severe illness than later infection with both of these agents -- 30 per cent of the children undergoing first infection with these agents will have some form of lower tract illness (21).

Another host factor which is ill defined at present is the individual diathesis for a particular clinical manifestation. For instance, there are certain children who will get repeated attacks of croup as the primary manifestation of non-bacterial respiratory infections regardless of the etiologic agents. In the three

clinical categories studied, approximately one third of the children with croup had a positive family history for croup and about 14 per cent of the cases without virus isolation also had a positive history for croup, and 12-23 per cent of children with and without virus isolation respectively, who were hospitalized with croup, had previous attacks.

The question of allergy has been often raised among clinicians when they see a child with repeated attacks of one form of respiratory infection or another since these children not infrequently later develop asthma or seem to have a higher chance of being an "allergic" child. In the present study, the cases from which there was no virus isolation generally had a higher incidence of positive family history for allergy. Then, whether the clinical response in a child with bronchiolitis was an allergic manifestation rather than a purely infectious process in this group without virus isolation is only a speculative question at the moment. Until the basic mechanism of hypersensitivity is more clearly elucidated, this very important aspect of host factors remains unexplained.

From the analysis of the cases studied, it can be noted that bronchiolitis cases and pneumonia have the highest frequency in the under-one-year age category. Croup was seen primarily in children under 4 years of age although the cases with H. influenza type B tended to be somewhat older.

The incidence by sex is not striking in bronchiolitis or pneumonia in that both males and females appear to be equally susceptible.

However, for croup, the male to female ratio (M:F) differs in that there seems to be a predilection for males in croup. In Rabe's study, M:F was 2.3:1 (92) and in Hartmann's study, it was 2.4:1 (47). Berg in his series of 850 cases of croup noted a ratio of 2.5:1 (10). A similar ratio was noted in the present study. Parrott noted a much higher incidence of 12:1 in favor of males (89). The exact significance of this observation is not known at the moment.

Do the findings in the present study indicate any particular etiologic association between a particular clinical manifestation with a certain viral agent or a group of agents? In other words, are there such entities as "croup viruses" or "bronchiolitis viruses"? And, if this is the case, how do the findings in the present study compare with those of the other investigators? Seventeen of the patients hospitalized with croup at the G-NHCH grew out various types of parainfluenza, particularly para-1. No other viral groups were associated with croup although in Parrott's studies, adenovirus, influenza virus and RS virus were all implicated with croup (87). It may be useful to point out that Rabe's (92) and Hartmann's studies (47), both of which were carried out here at the G-NHCH, show a remarkable similarity in the incidence of H. influenza type B croup. Rabe's series had 8.1 per cent H. influenza type B croup, Hartmann's, 8 per cent and the present study yielded 7.7 per cent.

Chanock has implicated RS virus with lower respiratory tract disease, notably bronchiolitis (18,22). Unfortunately, in

this study there was only 1 case of bronchiolitis associated with RS virus isolation, and therefore, no such conclusion can be drawn from the present series. However, serological studies indicated several cases infected with RS virus either in conjunction with the parainfluenza virus infection or in the cases where no other viral agents were isolated. The cases associated with parainfluenza isolations were all pneumonia cases and the cases without virus isolation were bronchiolitis cases. It is possible that the serological evidence of infection with RS virus in those cases associated with parainfluenza virus isolation could be due to concurrent infections with RS virus, which was not detected by our routine isolation method. Or, this finding could be due to purely an antibody response triggered by the active infection with parainfluenza viruses. No antigenic relationship between parainfluenza viruses and RS virus has yet been demonstrated. It would be of great interest if further studies could elucidate the mechanism of the rise in the antibody titer of RS virus in association with an active infection with parainfluenza viruses. At present, the most plausible interpretation for this is that the isolation techniques were not adequate enough to detect RS virus although it may have been active in certain instances.

Pneumonia seemed to be associated with a wider variety of etiologic agents and occasionally was associated with sporadic infection with whatever agent happened to be prevalent at a given time, i.e., in summer, one may have pneumonia with the predominant enterovirus.

As shown in Figures 1 and 2, there is a marked seasonal trend in illness due to myxoviruses. The peak incidence is in the winter. When longitudinal studies are carried out, fluctuating patterns are seen in prevalence of various agents. Thus, incidence of respiratory illness due to a particular virus is, in part, dependent on the prevalence of such an agent in the community at a given time. For instance, Chanock's group (18,22) in Washington, D.C., reported a significant association of RS virus with lower respiratory tract disease. One cannot make such an association based on the viral experiences in New Haven, since RS virus was not the most active agent here during the present study period. Wenner (117) and Wulff (119) in their longitudinal studies on etiology of respiratory infections observed that para-1 and -3 were the predominant agents in 1960-61 whereas there was a high incidence of RS virus infections associated with pneumonia and bronchiolitis the following year (1961-62). McLean was able to associate croup with parainfluenza-1 virus in the winters of 1961 and 1962 because Toronto experienced an "epidemic" of parainfluenza infections during that time (82,83). Vargosko and associates noted that during the epidemic period of Asian influenza in Washington, D.C., influenza A was associated with 35 per cent of croup illness as contrasted with no serologic evidence of influenza infection in the control group, thus suggesting the etiologic association of influenza A_2 virus with croup (110). One cannot make such an etiologic association if one were to base the findings from the New Haven area since during the period of the

present study, only 1 case of influenza A_2 has been isolated from a case of pneumonia.

One may conclude, then, by stating that in studying the etiology of respiratory infections, without the total perspective of the spectrum of the viral agents involved against the background of epidemiological findings, the results will only be partial and will not give the total answer.

SUMMARY

1. A total of 297 patients, hospitalized from June, 1961, through December, 1963, with bronchiolitis, croup or pneumonia, was studied. Viral agents were isolated from 11 per cent of bronchiolitis, from 18 per cent of croup and from 12 per cent of pneumonia cases.

2. The seasonal incidence of the viral agents associated with the respiratory illness generally followed the seasonal incidence of the over-all virus isolations as routinely carried out at the Virus Diagnostic Laboratory.

3. Viruses associated with bronchiolitis were parainfluenza, adenovirus, and RS virus. Croup was associated with all three types of parainfluenza but most frequently with para-1. Pneumonia was associated with para-1, 2, and 3, adenovirus, Coxsackie B-4 and B-5 as well as Echo-22; RS virus was detected in certain cases of pneumonia only by serologic evidence.

4. No significant difference was observed in the clinical expressions of respiratory infections with various viral agents.

5. Virus positive and virus negative groups were compared. The incidence of allergic history was consistently higher in the virus negative groups, but no other significant differences were observed.

APPENDIX

Seasonal Pattern of the Over-All Viral Activities and of Those Associated With Respiratory Illness

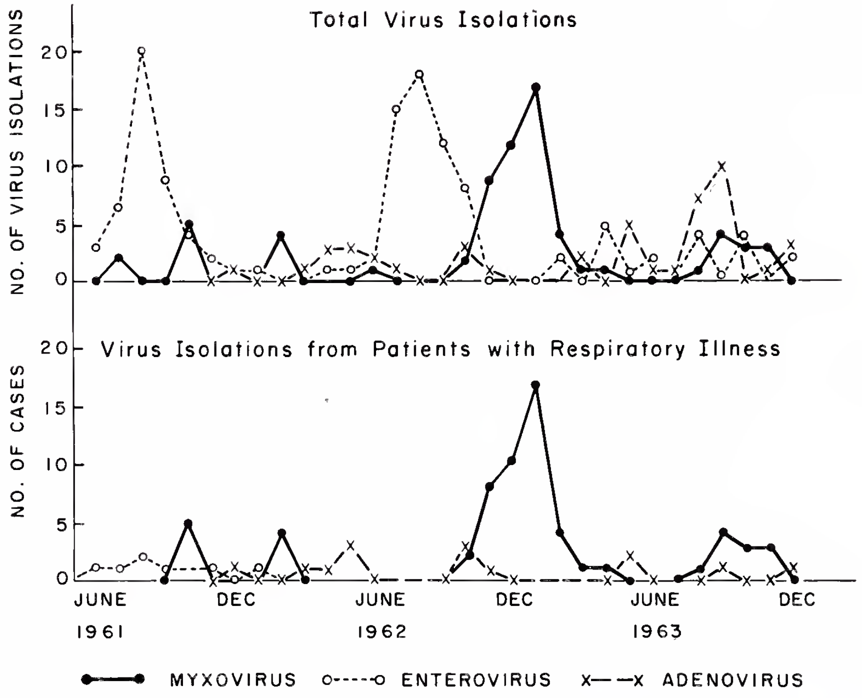

Figure 1

Recovery Ratio of Viruses According to Clinical Syndromes

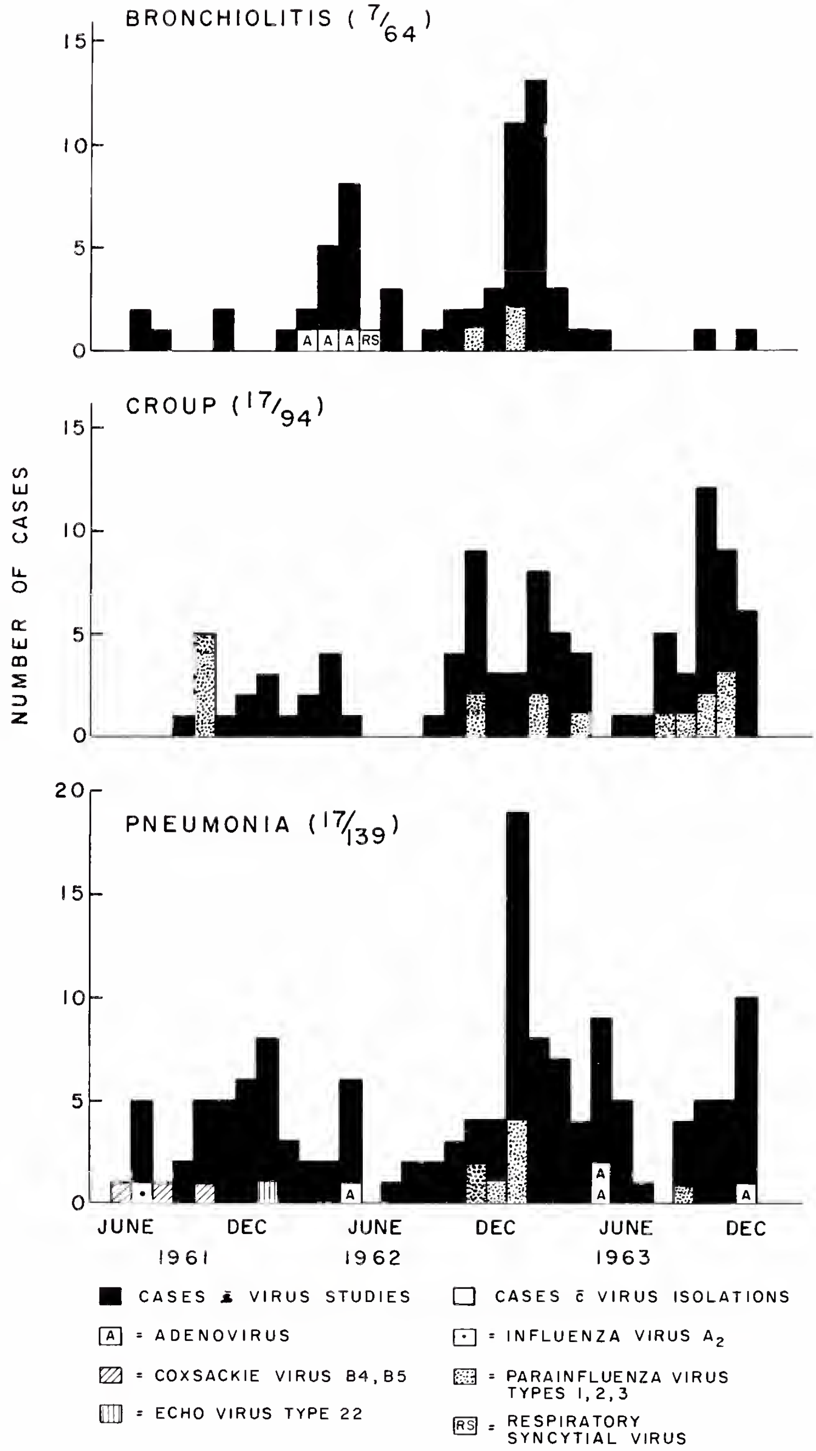

Figure 2

Age Distribution of Illness According to Clinical Syndromes

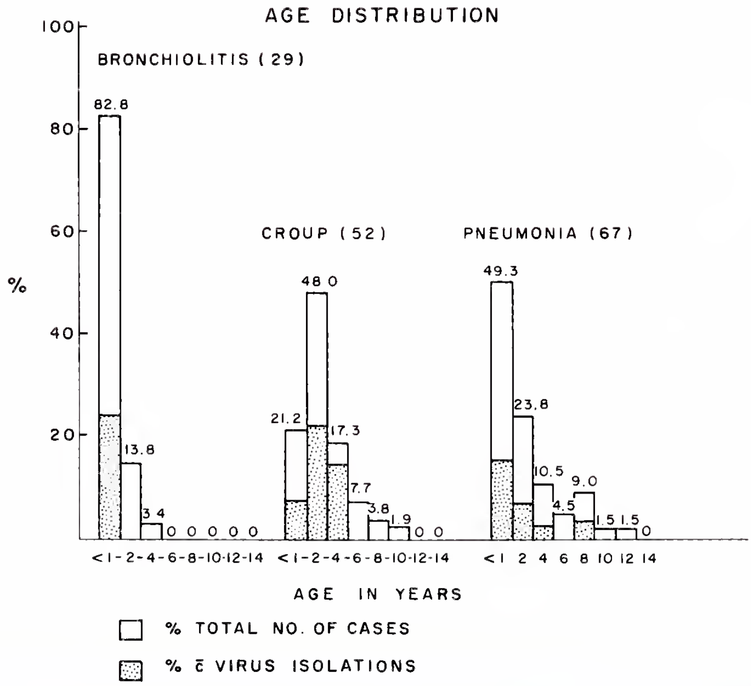

Figure 3

TABLE I

Isolations of Viral and Bacterial Agents from Cases of Bronchiolitis, Croup and Pneumonia

Agents Isolated	Per Cent of Isolations Bronchiolitis (29)	 Croup (52)	 Pneumonia (67)
Influenza A_2	-	-	1.5
Parainflu-1	10.3	19.2	7.5
Parainflu-2	-	9.6	1.5
Parainflu-3	-	3.8	3.0
RS*	3.4	-	-
Adeno-	10.3	-	7.5
Coxsackie B	-	-	4.5
Echo-22	-	-	1.5
H. Influ. B	-	7.7	1.5
Staphylococci	-	1.9	4.5
Pneumococci	31.0	21.0	35.8
No Pathogens	45.0	36.6	31.2

Number in ( ) indicates total number of cases studied.

* Two additional cases of bronchiolitis and three cases of pneumonia were diagnosed as RS virus infections by serological test. These were not included in the total per cent.

TABLE II

Dual Isolations - Number of Patients Yielding More Than One Agent

Agents Isolated	Bronchiolitis No. of Cases	Croup No. of Cases	Pneumonia No. of Cases
Influenza A_2	-	-	1
Parainfluenza-1	3 (1*)	10 (2*)	5 (3*) (2†)
Parainfluenza-2	-	5	1 (With adeno. See below)
Parainfluenza-3	-	2	2 (1*) (1†)
RS	1	-	-
Adenovirus	3 (1*)	-	5 (1*) (1 with para-2. See above)
Coxsackie B	-	-	3 (2*)
Echo-22	-	-	1
Total	7	17	17

Numbers in ( ) indicate cases of dual infection with bacteria or virus.

* - Pneumococci isolated concurrently from nose and/or throat swabs.

† - A greater than 4-fold antibody rise to RS virus.

TABLE III

Antibody Response in Children With and Without Virus Isolation

Serological Method Used	Viral Antigens	Numbers with Four-Fold or Greater Antibody Rises: Cases with Virus Isolations	Numbers with Four-Fold or Greater Antibody Rises: Cases without Virus Isolations
Hemagglutination-Inhibition	Influenza A	0	0
	Influenza B	0	0
	Para - 1	2*	0
	Para - 2	0	0
	Para - 3	3**	0
	DA	0	0
	Mumps	0	0
Complement Fixation	Adenovirus	0	0
	Reovirus	0	0
	RS	3	2
Total No. Cases Tested		10	17

* One case showed homologous rise. The other case showed heterogous rise with para-3 isolation.

** One case showed heterogous rise with para-1 isolation. The remaining 2 cases were homologous rise.

TABLE IV

Comparison of Virus Positive and Virus Negative Cases of Bronchiolitis (29)*

	Clinical Findings	Per Cent Showing Clinical Findings Virus Positive Cases (7)	 Cases without Virus Isolations (22)
	1. Initial Symptoms		
	Rhinorrhea	29	27
	"Cold" or coryza	14	27
	Cough	86	50
	Fever	14	32
	2. Findings at Admission		
Symptoms	Cough	14	45
	Gastrointestinal complaints	71	73
	Respiratory distress	100	77
Signs	Nasal erythema or discharge	43	36
	Pharyngeal erythema	43	59
	Cervical adenopathy	29	5
	TM erythema	29	0
	Rales or rhonchi	72	45
Temperature	< 38°C (Rectal)	86	66
	38° - 39°	14	19
	39°- 40°	0	14
WBC	< 10,000	0	32
	10,000-15,000	71	54
	15,000-20,000	29	14
	20,000-25,000	0	0
	> 25,000	0	0
	3. Duration of Fever (Days)		
	1 - 2	29	36
	3 - 4	14	5
	> 5	0	0
	4. Bacteriology		
	Pneumococci	28.6	40.9
	H. Influenza B.	-	-
	Staphylococci	-	-

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* Numbers in ( ) indicate total cases studied.

TABLE V

Comparison of Virus Positive and Virus Negative Cases of Croup (52)*

	Clinical Findings	Per Cent Showing Clinical Findings	
		With Virus Isolations (17)	Without Virus Isolations (35)
	1. Initial Symptoms		
	Rhinorrhea	12	23
	Hoarseness or stridor	18	6
	Barking cough	25	6
	Cough	31	26
	Fever	25	17
	2. Findings at Admission		
Symptoms	Croupy sounds	63	49
	Respiratory distress	81	54
	Gastrointestinal complaints	6	26
Signs	Pharyngeal erythema	69	60
	Epiglottis erythema	12	26
	Cervical adenopathy	12	20
	TM erythema	25	13
	Rales or rhonchi	12	26
Temperature	$<$ 38°C (Rectal)	13	34
	38° - 39°	31	29
	39° - 40°	31	34
	$>$ 40°	25	3
WBC	$<$ 10,000	50	26
	10,000-15,000	37	37
	15,000-20,000	13	17
	20,000-25,000	0	11
	$>$ 25,000	0	9
	3. Duration of Fever (Days)		
	1 - 2	56	53
	3 - 4	38	10
	$>$ 5	6	3
	4. Bacteriology		
	Pneumococci	11.8	31.4
	H. Influenza B	-	11.4
	Staphylococci	-	2.9
	5. Tracheotomy	6	14

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* See Table IV.

TABLE VI

Comparison of Virus Positive and Virus Negative Cases of Pneumonia (67)*

	Clinical Findings	Per Cent Showing Clinical Findings	
		With Virus Isolations (17)	Without Virus Isolations (50)
	1. Initial Symptoms		
	Rhinorrhea	19	22
	URI or coryza	25	10
	Cough	19	46
	Conjunctivitis	19	10
	Fever	56	20
	2. Findings at Admission		
Symptoms	Cough	38	36
	Gastrointestinal complaints	81	58
	Respiratory distress	38	64
Signs	Nasal erythema or discharge	38	44
	TM erythema	6	20
	Pharyngeal erythema	44	42
	Cervical adenopathy	6	40
	Dullness or B.S.	38	24
	Rales, rhonchi or wheezes	81	66
	Splenomegaly	12	0
Temperature	< 38°C (Rectal)	50	26
	38° - 39°	12	38
	39° - 40°	25	22
	> 40°	13	14
WBC	< 10,000	50	20
	10,000-15,000	12	34
	15,000-20,000	19	22
	20,000-25,000	7	16
	> 25,000	12	8
	3. Duration of Fever (Days)		
	1 - 2	44	64
	3 - 4	19	11
	≥ 5	6	2
	4. Bacteriology		
	Pneumococci	41.2	48
	H. Influenza B	-	2
	Staphylococci	-	6

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* See Table IV.

TABLE VII

Summary of Some of the Clinical Findings in Patients with Respect to Virus Isolation

	Clinical Syndromes					
	Bronchiolitis (29)		Croup (52)		Pneumonia (67)	
Clinical Findings	with virus isolation (7)	without virus isolation (22)	with virus isolation (17)	without virus isolation (35)	with virus isolation (17)	without virus isolation (50)
Age*	4 mos.	3.5 mos.	1 year	2 years	8 mos.	1 year
Sex (M:F)	4:3	4.3:3	2.4:1	2.3:1	1.1:1	1:1.1
Onset (days)	5	3	1	1	3	4
WBC*	13,050	11,725	9,725	11,200	9,700	11,850
Hospitalization (days)	9	4	3	3	4.5	5
Mortality** (%)	14	0	0	0	0	4
Family history with URI (%)	52	68	75	57	37	40
Family with croup	-	-	29	14	-	-
Previous history with croup			12	23		
Allergy history (%)	14	27	6	17	0	22
Associated disease (%)						
Asthma	0	9	None		0	8
CHD	14	0			19	6
Cystic fibrosis	0	0			6	4
Neoplastic	0	0			0	2

* Median value

** Cases which had associated disease such as CHD or glioma

Numbers in ( ) indicate total cases studied.

BIBLIOGRAPHY

1. Adams, J.M., Imagawa, D.T., and Zike, K.: Epidemic bronchiolitis and pneumonitis related to respiratory syncytial virus. J.A.M.A., 1961, 176, 1037.

2. Adams, J.M., Imagawa, D.T., and Zike, K.: Relationship of pneumonitis of infants to respiratory syncytial virus. Lancet, 1961, 2, 466.

3. Andrewes, C.H., Bang, F.B., Chanock, R.M., and Zhadnov, V.M.: Parainfluenza viruses 1, 2, and 3: Suggested names for recently described myxoviruses. Virology, 1959, 8, 129.

4. Beale, A.J., McLeod, D.L., Stackiw, W., and Rhodes, A.J.: Isolation of cytopathogenic agent from the respiratory tract in acute laryngotracheobronchitis. Brit. Med. J., 1958, 1, 302.

5. Beem, M., Wright, F.H., Hamre, D., Egerer, R., and Oehme, M.: Association of the chimpanzee coryza agent with acute respiratory disease in children. New Eng. J. Med., 1960, 263, 523.

6. Bell, J.A., Huebner, R.J., Rosen, L., Rowe, W.P., Cole, R.M., Mastrota, F.M., Floyd, T.M., Chanock, R.M., and Shvedoff, R.A.: Illness and microbial experiences of nursery children at Junior Village. Amer. J. Hyg., 1961, 74, 267.

7. Bell, J.A., Rowe, W.P., and Rosen, L.: Acute respiratory diseases of viral etiology: II Adenoviruses. Amer. J. Publ. Hlth., 1962, 52, 902.

8. Benyesh-Melnick, M., and Rosenberg, H.S.: The isolation of adenovirus type 7 from a fatal case of pneumonia and disseminated disease. J. Pediat., 1964, 64, 83.

9. Berenberg, W., and Kevy, S.: Acute epiglottitis in childhood: Serious emergency, readily recognized at bedside. New Eng. J. Med., 1958, 258, 870.

10. Berg, R.B.: Weight and sex of children hospitalized with infectious croup: An analysis of 850 cases. Pediatrics, 1961, 31, 18.

11. Berge, T.O., England, B., Mauris, C., Shuey, H.E., and Lennette, E.H.: Etiology of acute respiratory disease among service personnel at Ft. Ord, California. Amer. J. Hyg., 1955, 62, 283.

12. Bloom, H.H., Johnson, K.M., Jacobsen, R., and Chanock, R.M.: Recovery of parainfluenza viruses from adults with upper respiratory illness. Amer. J. Hyg., 1961, 74, 50.

13. Idem: Acute respiratory disease associated with Coxsackie A-21 virus infection: II. Incidence in military personnel: Observations in a nonrecruit population. J.A.M.A., 1962, 179, 120.

14. Blottner, R.J.: Comments on current literature: Acute laryngotracheobronchitis. J. Pediat., 1963, 62, 288.

15. Bukrinskaya, A.G., and Paktoris, E.A.: An outbreak of pneumonia caused by Type 1 hemadsorption virus. Acta Virol. (Eng.), 1960, 4, 184.

16. Chanock, R.M.: Association of a new cytopathogenic myxovirus with infantile croup. J. Exp. Med., 1956, 104, 555.

17. Idem: Recovery of a new type of myxovirus from infants with croup. Ann. N.Y. Acad. Sci., 1957, 67, 287.

18. Chanock, R.M., and Finberg, L.: Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA): II. Epidemiologic aspects of infection in infants and young children. Amer. J. Hyg., 1957, 66, 291.

19. Chanock, R.M., Mufson, M.A., Bloom, H.H., James, W.D., Fox, H.H., and Kingston, J.R.: Eaton agent pneumonia. J.A.M.A. 1961, 175, 213.

20. Chanock, R.M., Parrott, R.H., Cook, K., Andrews, B.E., Bell, J.A., Reichelderfer, T., Kapikian, A.Z., Mastrota, F.M., and Huebner, R.J.: Newly recognized myxoviruses from children with respiratory diseases. New Eng. J. Med., 1958, 258, 207.

21. Chanock, R.M., Parrott, R.H., Johnson, K.M., and Kapikian, A.Z.: Myxoviruses: Parainfluenza. Amer. Rev. Resp. Dis., 1963, 88 (Part 2), 1952.

22. Chanock, R.M., Parrott, R.H., Vargosko, A.J., Kapikian, A.Z., Knight, V., and Johnson, K.M.: Acute respiratory diseases of viral etiology: IV. Respiratory syncytial virus. Amer. J. Publ. Hlth., 1962, 52, 918.

23. Chanock, R.M., Roizman, B., and Myers, R.: Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA): I. Isolation, properties and characterization. Amer. J. Hyg., 1947, 66, 281.

24. Chanock, R.M., Vargosko, A., Luckey, A., Cook, M.K., Kapikian, A.Z., Reichelderfer, T., and Parrott, R.H.: Association of hemadsorption viruses with respiratory illness in childhood. J.A.M.A., 1959, 548.

25. Chany, C., Lepine, P. Lelong, M., Le-Tan-Vinh, Satge, P., and Virat, J.: Severe and fatal pneumonia in infants and young children associated with adenovirus infections. Amer. J. Hyg., 1958, 67, 367.

26. Cramblett, H.G.: Group-- present day concept. Pediatrics, 1960, 25, 1071.

27. Idem: Isolation of a cytopathogenic agent resembling the CA virus from an infant with croup. Pediatrics, 1958, 22, 56.

28. Cramblett, H.G., Kasel, J.A., Longmack, M., and Wilken, F.D.: Illnesses in children infected with an adenovirus antigenically related to types 9 and 15. Pediatrics, 1960, 25, 822.

29. Cramblett, H.G., Rosen, L., Parrott, R.H., Bell, J.A., Huebner, R.J., and McCullough, N.B.: Echo viruses associated with respiratory disease in children. Amer. J. Dis. Child., 1957, 94, 407.

30. Idem: Respiratory illness in six infants infected with a newly recognized Echo virus. Pediatrics, 1958, 21, 168.

31. Deinhardt, F., May, R.D., Calhoun, H.H., and Sullivan, H.E.: The isolation of adenovirus type 1 from a fatal case of viral "pneumonitis." A.M.A. Arch. Intern. Med., 1958, 102, 816.

32. Dingle, J.H., Badger, G.F., Feller, A.E., Hodges, R.G., Jordan, W.S., Jr., and Rammelkamp, C.H., Jr.: A study of illness in a group of Cleveland families: II. Incidence of the common respiratory diseases. Amer. J. Hyg., 1953, 58, 31.

33. Dingle, J.H., and Feller, A.E.: Noninfluenzal viral infections of the respiratory tract. New Eng. J. Med., 1956, 254, 465.

34. Eichenwald, H.: "The stuffy nose syndrome" of premature infants: An example of bacterial-viral synergism (Abstract). Amer. J. Dis. Child., 1958, 96, 438.

35. Eichenwald, H.F., and Kotsevalov, O.: Immunologic response of premature and full-term infants to infection with certain viruses. Pediatrics, 1960, 25, 829.

36. Eichenwald, H.F., Kotsevalov, O., and Fasso, L.A.: Another example of bacterial-viral interaction: The "cloud baby" (Abstract). Amer. J. Dis. Child., 1959, 98, 432.

37. Evans, A.S.: Adenovirus infections in children and young adults: With comments on vaccination. New Eng. J. Med., 1958, 259, 464.

38. Idem: Infection with hemadsorption virus in University of Wisconsin students. New Eng. J. Med., 1960, 263, 233.

39. Idem: Latent adenovirus infections of the human respiratory tract. Amer. J. Hyg., 1958, 67, 256.

40. EXPERT Committee on Respiratory Virus Diseases. World Health Organization Technical Report Series No. 170, 1959.

41. Fukumi, H., Nishiwara, F., and Kitayama, T.: A pneumotropic virus from mice causing hemagglutination. Jap. J. Med. Sci. Biol., 1954, 7, 345.

42. Gardner, P.S., Stanfield, J.P., Wright, A.E., Court, S.D.M., and Green, C.A.: Viruses, bacteria and respiratory disease in children. Brit. Med. J., 1960, 1, 1077.

43. Gordon, R.B., Lennette, E.H., and Samdrock, R.S.: The varied clinical manifestations of Coxsackie virus infections: Observations and comments on an outbreak in California. Arch. Int. Med., 1959, 103, 63.

44. Gutekusnst, R.R., and Heggie, A.D.: Viremia and viruria in adenovirus infections: Detection in patients with rubella or rubelliform illness. New Eng. J. Med., 1961, 264, 374.

45. Hamparian, V.V., Ketler, A., Hilleman, M.R., Reilly, C.M., McClelland, L., Cornfeld, D., and Stokes, J., Jr.: Studies of acute respiratory illnesses caused by respiratory syncytial virus: 1. Laboratory findings in 109 cases. Proc. Soc. Exp. Biol. Med., 1961, 106, 717.

46. Hamre, D., Lashof, J.C., Marshall, L.J., Cassidy, J.E., Smith, M., and Bennet, R.: A study of viruses implicated in acute respiratory disease in Chicago from October, 1958, to June, 1959. Amer. Rev. Resp. Dis., 1961, 83, 38.

47. Hartmann, H.S.: Infectious croup in New Haven - Review of cases and survey of antibodies against two new croup viruses. M.D. Thesis - Yale University School of Medicine, 1959.

48. Health Statistics, U. S. National Health Survey: Acute conditions, incidence and associated disability. Public Health Service Publ. No. 584 - B18, June, 1960.

49. Hilleman, M.R.: Epidemiology of adenovirus respiratory infections in military recruit populations. Ann. N. Y. Acad. Sci., 1957, 67, 262.

50. Idem: Respiratory syncytial virus. Amer. Rev. Resp. Dis., 1963, 88 (Part 2), 181.

51. Idem: The parainfluenza viruses of man. Ann. N.Y. Acad. Sci., 1962, 103, 564.

52. Hilleman, M.R., Hamparian, V.V., Ketler, A., Reilly, C.M., McClelland, L., Cornfeld, D., and Stokes, J., Jr.: Acute respiratory illnesses among children and adults: Field study of contemporary importance of several viruses and appraisal of the literature. J.A.M.A., 1962, 180, 445.

53. Hilleman, M.R., and Werner, J.H.: Recovery of new agent from patients with acute respiratory illness. Proc. Soc. Exp. Biol. Med., 1954, 85, 183.

54. Holland, W.W., Tanner, E.I., Pereira, M.S., and Taylor, C.E.D.: A study of the aetiology of respiratory disease in a general hospital. Brit. Med. J., 1960, 1, 1917.

55. Horsfall, F.L.: Viral infections of the respiratory tract. Amer. Rev. Resp. Dis., 1959, 80, 315.

56. Horstmann, D.M., and Hsiung, G.D.: Myxovirus infection and respiratory illness in children. Cl. Pediat., 1963, 2, 378.

57. Hsiung, G.D., Isacson, P., and McCollum, R.W.: Studies of a myxovirus isolated from human blood. I. Isolation and properties. J. Immuno., 1962, 88, 284.

58. Hsiung, G.D., Isacson, P., and Tucker, G.: Studies of parainfluenza viruses. II Serologic interrelationships in humans. Yale J. Biol. Med., 1963, 35, 534.

59. Hsiung, G.D., Pinheiro, F., and Gabrielson, M.O.: The virus diagnostic laboratory: Functions and problems based on three years' experience. Yale J. Biol. Med., 1963, 36, 104.

60. Huebner, R.J. (Chairman): Viruses in search of disease. Ann. N. Y. Acad. Sci., 1957, 67, 209.

61. Huebner, R.J., Rowe, W.P., and Chanock, R.M.: Newly recognized respiratory tract viruses. Ann. Rev. Microbiol. 1958, 12, 49.

62. Huebner, R.J., Rowe, W.P., Ward, T.G., Parrott, R.H., and Bell, J.A.: Adenoidal-pharyngeal-conjunctival agents: A newly recognized group of common viruses of the respiratory system. New Eng. J. Med., 1954, 251, 1077.

63. Isacson, P., McCollum, R.W., and Hsiung, G.D.: Studies of a myxovirus isolated from human blood. III Serologic reactions in persons with viral hepatitis. J. Immunol., 1962, 88, 300.

64. Jackson, G.G.: Viruses of the upper respiratory tract. Annual Rev. Med., 1956, 7, 1.

65. Jensen, K.E., Minuse, E., and Ackermann, W.W.: Serologic evidence of American experience with newborn pneumonitis virus (type Sendai). J. Immunol., 1955, 75, 71.

66. Johnson, K.M., Bloom, H.H., Mufson, M.A., and Chanock, R.M.: Acute respiratory disease associated with Coxsackie A-21 virus infection: I. Incidence in military personnel; Observations in a recruit population. J.A.M.A., 1962, 179, 112.

67. Johnson, K.M., Chanock, R.M., Cook, K., and Huebner, R.J.: Studies of a new human hemadsorption virus. I. Isolation, properties and characterization. Amer. J. Hyg., 1960, 71, 81.

68. Jordan, W.S.: The frequency of infection with adenoviruses in a family study population. Ann. N.Y. Acad. Sci., 1957,67, 273.

69. Idem: Occurrence of adenovirus infections in civilian population. A.M.A. Arch. Intern. Med., 1958, 101, 54.

70. Jordan, W.S., Badger, G.F., and Dingle, J.H.: A study of illness in a group of Cleveland families: IV. Acquisition of type-specific adenovirus antibodies in the first five years of life: Implications for the use of adenovirus vaccine. New Eng. J. Med., 1958, 258, 1041.

71. Kapikian, A.Z., Mastrota, F.M., Johnson, K.M., Huebner, R.J., and Chanock, R.M.: An outbreak of febrile illness and pneumonia associated with respiratory syncytial virus infection. Amer. J. Hyg., 1961, 74, 234.

72. Kapikian, A.Z., Chanock, R.M., Bell, J.A., Reichelderfer, T.E., and Huebner, R.J.: A study of the hemadsorption viruses (parainfluenzae) and other viruses in children with and without respiratory disease. Pediatrics, 1960, 26, 243.

73. Kendall, E.J.C., and Cook, G.T.: Acute respiratory infections in children. Isolation of Coxsackie B virus and adenovirus during a sruvey in a general practice. Brit. Med. J., 1960, 2, 1180.

74. Kevy, S.: Current concepts: Croup. New Eng. J. Med., 1964, 270, 464.

75. Kim, H.W., Vargosko, A.J., Chanock, R.M., and Parrott, R.H.: Para-influenza 2 (CA) virus: Etiologic association with croup. Pediatrics, 1961, 28, 614.

76. Kjellen, L., Sterner, G., and Svedmyr, A.: On the occurrence of adenoviruses in Sweden. Acta Paediat. (Stockholm), 1957, 46, 164.

77. Kripke, S.: Infectious pneumonias of early infancy. Amer. Dis. Child., 1961, 102, 153.

78. Kuroya, N., and Ishida, M.: Newborn virus pneumonitis (type Sendai). II. Isolation of new virus possessing hemagglutin in activity. Yokohoma M. Bull., 1953, 4, 217.

79. Lennette, E.H., Stallones, R.A., and Holguin, A.H.: Pattern of respiratory virus infections in army recruits. Amer. J. Hyg., 1961, 74, 225.

80. Lerner, A.M., Klein, J.O., Levin, H.S., and Finland, M.: Infections due to Coxsackie virus group A, type 9, in Boston, 1959, with special reference to exanthema and pneumonia. New Eng. J. Med., 1960, 263, 1265.

81. McClelland, L., Hilleman, M.R., Hampairan, V.V., Ketler, A., Reilly, C.M., Cornfeld, D., and Stokes, J., Jr.: Studies of acute respiratory illnesses caused by respiratory sycytial virus. 2. Epidemiology and assessment of importance. New Eng. J. Med., 1961, 264, 1169.

82. McLean, D.M., Roy, T.E., O'Brien, M.J., Wylie, J.C., and McQueen, E.J.: Parainfluenza virus in association with acute laryngotracheobronchitis. Canad. Med. Ass. J., 1961, 85, 290.

83. McLean, D.M., Edwards, H.E., McQueen, E.J., and Petite, H.E.: Myxovirus infections in acute laryngotracheobronchitis, Toronto, 1961-62. Canad. Med. Ass. J., 1962, 87, 998.

84. Mogabgab, W.J.: Viruses associated with upper respiratory illness in adults. Ann. Intern. Med., 1963, 59, 306.

85. Morris, J.A., Blount, R.E., and Savage, R.E.: Recovery of cytopathogenic agent from chimpanzees with coryza. Proc. Exp. Biol. Med., 1956, 92, 544.

86. Parrott, R.H., Vargosko, A.J., Kim, H.W., Bell, J.A., and Chanock, R.M.: Respiratory diseases of viral etiology. III. Myxoviruses: Parainfluenza. Amer. J. Publ. Hlth., 1962, 52, 907.

87. Parrott, R.H., Vargosko, A.J., Kim, H.W., Chanock, R.M.: Clinical syndromes among children. Amer. Rev. Resp. Dis., 1963, 88 (Part 2), 73.

88. Parrott, R.H., Vargosko, A.J., Kim, H.W., Cumming, C., Turner, H., Huebner, R.J., and Chanock, R.M.: Respiratory syncytial virus: II. Serologic studies over a 34-month period of children with bronchiolitis, pneumonia, and minor respiratory diseases. J.A.M.A., 1961, 176, 653.

89. Parrott, R.H., Vargosko, A.J., Luckey, A., Kim, H.W., Cumming, C., and Chanock, R.M.: Clinical features of infection with hemadsorption viruses. New Eng. J. Med., 1959, 260, 731.

90. Philipson, L.: Aetiology of non-diphtheritic croup. I. Bacteriologic and serologic investigation. Acta Paediat. (Stockholm), 1958, 47, 265.

91. Idem: Aetiology of non-diphtheritic croup. II. Virologic investigation. Ibid., 611.

92. Rabe, E.F.: Infectious croup. I. Etiology. Pediatrics, 2, 1948, 255.

93. Idem: Infectious croup. II. "Virus" croup. Ibid., 415.

94. Idem: Infectious croup. III. Hemophilus influenza type B croup. Ibid., 559.

95. Reicherlderfer, T.E., Chanock, R.M., Criaghead, J.E., and Huebner, R.J.: Infection of human volunteers with Type 2 hemadsorption virus. Science, 1958, 128, 779.

96. Reilly, C.M., Stokes, J., Jr., Hamparian, V.V., and Hilleman, M.R.: Echo virus, type 25, in respiratory illness. J. Pediat., 1963, 62, 538.

97. Reilly, C.M., Stokes, J., Jr., McClelland, L., Cornfeld, D., Hamparian, V.V., Ketler, A., and Hilleman, M.R.: Studies of acute respiratory illnesses caused by respiratory syncytial virus: 3. Clinical and laboratory findings. New Eng. J.Med., 1961, 264, 1176.

98. Robbins, F.C., and Weller, T.H.: Application of tissue culture methods to the study of viral infections. Pediatrics, 1954, 13, 283.

99. Robinson, R.Q., Hoshiwara, I., Schaeffer, M., Gorrie, R.H., and Kaye, H.S.; A survey of respiratory illnesses in a population. I. Viral studies. Amer. J. Hyg., 1962, 75, 18.

100. Rosen, L., Hovis, J.F., Mastrota, F.M., Bell, J.A., and Huebner, R.H.: An outbreak of infection with a type 1 reovirus among children in an institution. Amer. J. Hyg., 1960, 71, 206.

101. Rowe, D.S., and Michaels, D.T.: Isolation of the respiratory syncytial virus from a patient with pneumonia. Pediatrics, 1960, 26, 623.

102. Rowe, W.P., Huebner, R.J., Gilmore, L.K., Parrott, R.H., and Ward, T.G.: Isolation of a cytopathogenic agent from human adenoids undergoing spontaneous degeneration. Proc. Soc. Exp. Biol. Med., 1953, 84,570.

103. Schults, I., Gundelfinger, B., Rosenbaum, M., Woolridge, R., and DeBarry, P.: Comparison of clinical manifestations of respiratory illness due to Asian strain influenza, adenovirus and unknown cause. J. Lab. Clin. Med., 1960, 55, 497.

104. Siegel, W., Spencer, F.J., Smith, D.J., Toman, J.M., Skinner, W.F., and Marx, M.B.: Two new variants of infection with Coxsackie virus group B., type 5, in young children: A syndrome of lymphadenopathy, pharyngitis and hepatomegaly or splenomegaly or both, and one of pneumonia. New Eng. J. Med., 1963, 268, 1210.

105. Sterner, G.: Atypical pneumonia in an infant, associated with APC virus infection. Acta Paediat. (Stockholm), 1956, 45, 449.

106. Idem: Infections with adenovirus type 7 in children and their relationship to acute respiratory disease. Acta Paediat. (Stockholm), 1959, 48, 287.

107. Stuart-Harris, C.H.: Influenza and other virus infections of the respiratory tract, The Williams and Wilkins Co., Baltimore, Md., 1953.

108. van der Veen, J.: The role of adenoviruses in respiratory disease. Amer. Rev. Resp. Dis., 1963, 88 (Part 2), 167.

109. van der Veen, J., and Smear, F.A.A.M.: Infections with parainfluenza viruses in children with respiratory illnesses in Holland. Amer. J. Hyg., 1961, 74, 326.

110. Vargosko, A.J., Chanock, R.M., Huebner, R.J., Luckey, A., Kim, H.W., Cumming, C., and Parrott, R.H.: Association of type 2 hemadsorption (parainfluenza 1) virus and Asian influenza A virus with infectious croup. New Eng. J. Med., 1959, 261, 1.

111. Vargosko, A.J., Chanock, R.M., Kim, H.W., and Parrott, R.H.: Contribution of adenovirus infection to childhood respiratory tract illness. Amer. J. Dis. Child., 1961, 102, 501.

112. Vargosko, A.J., Kim, H.W., Parrott, R.H., and Chanock, R.M.: Association of Coxsackie B-5 virus with minor respiratory tract illness in children. Amer. J. Dis. Child., 1962, 104, 539.

113. Vogel, J., and Shelekov, A.: Adsorption-hemagglutination of influenza virus in monkey kidney cells. Science, 1957, 126, 358.

114. von Euler, L., Kantor, F.S., and Hsiung, G.D.: Studies of parainfluenza viruses. I. Clinical, pathological and virologic observations. Yale J. Biol. Med., 1963, 35, 523.

115. Wenner, H.A., Beran, G.W., Weston, J., and Chin, T.D.Y.: The epidemiology of acute respiratory illness; I. Observations on adenovirus infections prevailing in a group of families. J. Infect. Dis., 1957, 101, 275.

116. Wenner, H.A., Christodoupoulou, G., Weston, J., Marsh, A., and Liu, C.: The epidemiology of acute respiratory diseases. II. Risk of infection among infants and family associates from viruses accompanying respiratory illnesses. Pediatrics, 1961, 28, 886.

117. Wenner, H.A., Christodoulopoulou, G., Weston, J., Tucker, V., and Liu, C.: The etiology of respiratory illnesses occurring in infancy and childhood. Pediatrics, 1963, 31, 4.

118. Wood, S.H., Buddingh, G.J., and Abberger, B.F., Jr.: An inquiry into the etiology of acute bronchiolitis of infants. Pediatrics, 1954, 13, 363.

119. Wulff, H., Kidd, P., and Wenner, H.A.: Etiology of respiratory infections. Further studies during infancy and childhood. Pediatrics, 1964, 33, 30.

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